IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Jay A. Goldstein, Michael Rothman, and Whe-Yong Lo		
Serial No.:	10/691,928	Art Unit:	1616
Filed:	October 23, 2003	Examiner:	Nathan W. Schlientz
For:	*ANTIFUNGAL FORMULATIONS*		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Sir:

This is a reply brief to the Examiner's Answer mailed December 7, 2009, in the above-referenced application. Submitted with this Reply Brief is a Request for Oral Hearing. The Commissioner is hereby authorized to charge $540.00 the fee for a Request for Oral Hearing for a small entity, to Deposit Account No. 50-3129.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The Examiner confirmed that the grounds for appeal provided in the Appeal Brief filed on November 13, 2009 are correct.

(7) ARGUMENT

Appellants affirm all of the arguments made in the Appeal Brief.

I. Claims rejected under 35 U.S.C. § 102

In any claim analysis, the Examiner must consider the claim as a whole. The prior art must anticipate the claim as a whole, not disclose some limitations in the claims.

Claim 1 recites two limitations which distinguish the claimed formulation from the prior art formulations:

(i) the formulation contains a therapeutically effective amount of a low to low-medium potency steroidal anti-inflammatory causing minimal skin atrophy, striae and hypopigmentation, in a concentration between 0.01 wt% and 5.0 wt%, and having a higher potency than 1 wt% hydrocortisone, and

(ii) a carrier suitable for administration of the antifungal compound and the steroidal anti-inflammatory to the skin, wherein the composition does not cause the steroids to penetrate the skin and cause undesirable local side effects.

In order to make a determination regarding anticipation, the prior art must disclose not only the active agents but also the functional limitations recited in the claims. For a particular composition, the functional limitations provide that (a) the concentration of the low-mid potency steroid is selected such that it is therapeutically effective yet causes minimal skin atrophy, striae

and hypopigmentation, and (b) the selected steroid, in combination with the antifungal and carrier, when formulated to arrive at the claimed composition, does not cause the steroid to penetrate the skin and cause undesirable local side effects.

Thus, the claims provide compositions which require selecting the steroid, the concentration of the steroid as well as the carrier material such that the functional limitations disclosed above are met. This is not disclosed in any of the prior art references for the reasons set forth below.

(1) Claims 1 and 8-13 in view of Quigley

Quigley describes topical compositions useful in treating fungal diseases that comprise an antifungal agent and an anti-inflammatory steroid. See, e.g., column 1, line 66-column 2, line 27. Suitable steroids are provided in a laundry list of formulations at col. 4, line 55 until col. 5, line 51. Quigley lists the steroids in their order of potency. Of note is the fact the steroid formulations are accompanied by the concentration of the steroid in the formulation. The laundry list in Quigley clearly shows that the type of carrier and the concentration of the steroid determine the potency of the resulting formulation.

Quigley is not concerned with providing a formulation containing low-mid potency steroid in a concentration that it is therapeutically effective yet causes minimal skin atrophy, striae and hypopigmentation, as is exemplified by his repeated disclosure of 0.064 wt% betamethasone dipropionate cream as a preferred formulation. See Quigley, Examples 1-7. The list of formulations at col. 4, line 55 to col. 5, line 51 discloses that betamethasone dipropionate cream having a betamethasone dipropionate concentrate of 0.05%, which is lower than the concentration of the formulation described in Examples 1-7, is characterized as a class 2 steroid,

i.e., highly potent. Therefore, a cream containing 0.064% betamethasone dipropionate is at least a class 2 steroid, if not a class 1.

Quigley expressly states "the amount of steroid required will vary depending upon its potency, i.e., the more potent the steroid, the less needed, and vice versa. Quigley teaches that in the event a less potent steroid is selected, more of it should be used (col. 5, lines 53-56). Therefore, there is no direction in Quigley for example to select a low potency steroid like 0.02% betamethasone dispropionate in a lotion, and use 0.02% of the steroid. Rather, Quigley directs one to increase the concentration of the steroid. Quigley, col. 5, lines 53-56. This is exemplified in Example 10, where Quigley discloses 0.064 wt% betamethasone dipropionate lotion. The concentration of betamethasone dipropionate in the lotion in Example 10 is about three times the concentration of "betamethasone dipropionate lotion 0.02%" classified in Quigley, col. 5 as having a potency of 5. As one of ordinary skill in the art is aware, the potency of a steroid can be enhanced by increasing its concentration. See Goon, *Bulletin for Medical Practitioner*, 11(1) (a copy of which is attached) which was submitted with the response filed on July 30, 2007. In fact, betamethasone dipropionate lotion containing 0.064% betamethasone dipropionate is classified as a potent steroid, not the low to low-medium potency steroid required by the claims.

Quigley teaches one to increase the potency of the steroid in the event one selects a low potency steroid as disclosed in his list, by increasing its concentration. Increasing the potency of low potency steroids by increasing their concentration also increases their ability to penetrate the skin since high potency steroids penetrate the skin, likely resulting in the adverse side effects that the claimed formulations avoid.

The Examiner alleges Table G, in which Quigley disclose a lotion comprising a steroid having a concentration of 0.01 to 2.5 wt %, preferably 0.01 to 0.1 wt% steroid, anticipates the claims. As discussed above, Quigley teaches that for lotions, the preferred concentration of betamethasone dipropionate is 0.064% (*see* the discussion above with respect to Example 10), which is a potent or highly potent steroid when formulated as a lotion or cream. Appellants further note that the specific formulation disclosed in Table G contains a combination of petrolatum, cetyl alcohol, stearic acid and propylene glycol, the combination of which is disclosed for example, as providing enhanced penetration of drug molecules in the skin. See Shah, col. 1, lines 55-66 (citing U.S. Patent No. 4,775,678).

Quigley does not disclose the formulations as claimed, which do not cause the steroids to penetrate the skin and thus avoid adverse side effects. In fact, Quigley referring to the formulations described therein states "the test formulations significantly exceeded Lotrisone with respect to epidermal deposition of BMD, but penetration of the epidermis by BMD in the Lotrisone formulation proved to be significantly higher than shown for the formulations of the present invention". Quigley, col. 18, lines 39-43. A desire to minimize penetration of the steroid through the epidermis does not meet the limitation "wherein the composition does not cause the steroid to penetrate the skin". Examiner's Answer mailed December 7, 2009, para. bridging pages 3 and 4.

There is no recognition that the potency of the steroidal anti-inflammatory is the cause of the side effects and can be eliminated not only by selecting the carrier, but also by selecting a narrow class of steroidal anti-inflammatories in the concentration range recited in the claims.

The combination of these selections provides a composition as claimed, which causes minimal skin atrophy, striae and hypopigmentation, and does not cause the steroids to penetrate the skin and cause undesirable local side effects. Further, there is no recognition that formulations containing the narrow class of steroids in the claims can be therapeutically effective while avoiding adverse side effects. Accordingly, claim 1 is novel over Quigley. Claims 8-13, which depend from claim 1, are novel over Quigley for at least the reasons discussed above.

2. Claims 1-3, 8-13 and 17 in view of Burnett

Claims 1-3, 8-11, 13, and 17

Claim 1 explicitly recites "wherein the composition does not cause the steroids to penetrate the skin and cause undesirable local side effects". Thus, any carriers used to deliver the active agents must be selected either by type and/or concentration, such that skin penetration is avoided.

Burnett describes compositions for topical delivery of a medicament, which require the use of a penetration enhancer, to deliver more of the active agent across the skin. See abstract, col. 2, lines 9-11 and page 8, para. 0036. Thus, Burnett does not disclose the formulations defined by claims 1-3, 8-11, 13 and 17.

The Examiner alleges that although Burnett refers to the solvent propylene glycol as a penetration enhancer/solvent, they clarify the desire to prevent *permeation of the medicament through the skin and into the receptor*, resulting in diminished side effects. Examiner's Answer mailed December 7, 2009, page 5 (emphasis added). The Examiner might be correct in the assertion that Burnett does not desire the compositions disclosed therein to permeate through the

skin and into a receptor, however, the claims specify that the composition does not cause the active agent to penetrate the skin. Burnett teaches that the compositions described therein cause the active agent to penetrate the skin. For example, Burnett:

> "The amounts of each of the components of the present composition are typically those amounts effective to accomplish the purpose of that ingredient. For example, the amount of penetration enhancer is typically a penetration enhancing effective amount". *See* Burnett, col., 3, lines 26-31.

Further, Burnett in col. 8, lines 29-59 discloses that the composition in example 1 delivers less of the active agent to a receptor, than NIZORAL® (which could translate to less systemic toxicity). However, the formulation delivers greater amount of the drug to the epidermis and the dermis. As would be understood by one of ordinary skill in the art, a drug is considered to penetrate the skin when it crosses the stratum corneum i.e., the outermost layer of the epidermis. The formulations disclosed in Burnett deliver the active agent to the dermis, a skin layer below the epidermis. One of ordinary skill in the art would consider this a disclosure of active agent having penetrated the skin. Therefore, the Examiner's assertion that the composition of Burnett do not penetrate the skin, is incorrect. Examiner's Answer mailed December 7, 2009, page 5.

Further, the Examiner alleges the claimed compositions can penetrate the skin but not cause undesirable local side effects, or not penetrate the skin but cause undesirable local side effects and still be within the scope of the claims. Examiner's Answer mailed December 7, 2009, paragraph bridging pages 11 and 12. Appellants respectfully disagree with the Examiner's interpretation of the claim language. Taking the plain meaning of the words in the claims, the

conjunction "and" connects "penetrate the skin" with "cause local side effect". Thus, the claimed composition prevents both events from occurring, not one or the other.

For at least the reasons stated above, Burnett does not disclose the formulation defined by claims 1-3, 8-11, 13 and 17, which does not cause the steroids to penetrate the skin and cause undesirable local side effects. Therefore, claims 1-3, 8-11, 13 and 17 are novel over Burnett.

Claim 12

Claim 12 depends from claim 11, and specifies that the solvent is selected from a group of solvents including propylene glycol.

The Examiner noted that Burnett requires a penetration enhancer selected from the group consisting of alcohol and propylene glycol, and that propylene glycol is listed in claim 12. Examiner's Answer mailed December 7, 2009, paragraph bridging pages 4 and 5. However, for at least the reasons set forth above with respect to claims 1-3, 8-11, 13, and 17, claim 12 is novel over Burnett.

As noted above, the limitation "wherein the composition does not cause the steroids to penetrate the skin and cause undesirable local side effects" provides that any carriers used to deliver the active agents must be selected either by type and/or concentration, such that skin penetration is avoided. Burnett does not anticipate the claims merely because it lists a similar excipient as Appellants. Pharmaceutical excipients are selected based on the desired function and used in the concentrations effective to accomplish that function. A chemical does not have penetration enhancing effects merely by being present in a formulation. It must be present in that formulation in

an amount effective to enhance penetration. That is why Burnett for example, specifically states "For example, the amount of penetration enhancer is typically a penetration enhancing effective amount". *See* Burnett, col., 3, lines 26-31. Implicitly, there are amounts of the same compound which would not be effective in enhancing penetration. The Examiner's attention is also drawn to Shah, which states:

> "It is well known that the effectiveness of a penetration enhancer depends on the type of drug molecule and the composition of the formulation. Thus, in developing a topical formulation, the identification of an enhancer is only the first step, because reduction in penetration can occur as a multicomponent formulation is developed". See Shah, paragraph bridging col. 2 and 3.

Therefore, the disclosure of an excipient in Burnett, which is recited in claim 12, is not tantamount to a disclosure of the claimed formulation, which does not cause the steroids to penetrate the skin. Therefore, claim 12 is novel over Burnett.

II. Claims rejected under 35 U.S.C. § 103

(1) Claims 1-3 and 7-17 in view of Quigley

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims. For at least the reasons set forth above, Quigley does not disclose or suggest the claimed formulation.

Moreover, for at least the reasons stated above, Quigley teaches away from the claimed composition. A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the Appellants.

As discussed above, Quigley, in the working examples, directs one to increase the potency and hence dermal penetration of the steroids. One of ordinary skill in the art reading Quigley would be motivated to prepare high or medium-high potency formulations, not the low or low-medium potency formulations required by the claims, and thus would be lead in a direction divergent from the path Appellants have taken. Accordingly, claim 1 is not obvious over Quigley. Claims 2, 3, and 7-13 and 17, which depend from claim 1, are not obvious over Quigley for at least the reasons discussed above.

Claims 14-16 are drawn to a method of treating a fungal disease comprising administering to a subject in need thereof the composition of any of claims 1-13 or 17, with a thin application of the composition two times per day to the affected areas. For the reasons discussed above with respect to claims 1-3, 7-13, and 17, claims 14-16 are not obvious over Quigley.

(2) Claims 1-13 and 17 in view of Burnett and Shah

For at least the reasons stated above, Burnett does not disclose the composition defined by claim 1. Shah discloses a gel formulation for topical administration with enhanced skin penetration properties comprising a therapeutically effective amount of an imidazole antifungal agent. Shah, Abstract. Shah teaches formulations that enhance penetration of the active agent through the skin in contrast to the claimed formulations. Shah fails to cure the deficiencies in Burnett. The Examiner has not established a *prima facie* case of obviousness. Therefore, claims 1-13 and 17 are not obvious over Burnett and Shah.

The modification of the disclosure in Shah and Burnett to arrive at the claims is impermissible

There is no motivation to modify the disclosure in Burnett or Shah to arrive at the composition defined by claim 1. Burnett and Shah disclose compositions which cause the active agents disclosed therein to penetrate the skin. In order to arrive at the formulation defined by claim 1, one would have to modify the formulations in Burnett and Shah alone or in combination, to provide formulations which do not cause the active agent to penetrate the skin. Such a modification would render the formulation disclosed in Shah and Burnett unsatisfactory for their intended purpose. Burnett requires penetration of the skin by the active agent disclosed therein. *See* Burnett, col. 3, lines 28-30. Shah requires a high degree of penetration in order to enable the active agent reach hard-to-reach fungal infections. *See* Shah, col. 1, lines 50-55 and col. 4, lines 28-30. Therefore, the modification is impermissible. *See* MPEP § 2143.01(V): "If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification". *See* also MPEP 2101(VI):

> "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. (citation omitted) (Claims were directed to an oil seal comprising a bore engaging portion with outwardly biased resilient spring fingers inserted in a resilient sealing member. The primary reference relied upon in a rejection based on a combination of references disclosed an oil seal wherein the bore engaging portion was reinforced by a cylindrical sheet metal casing. **Patentee taught the device required rigidity for operation, whereas the claimed invention required resiliency**. The court reversed the rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary

reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." (emphasis added).

Here, the claims specify that the composition does not cause the active agent to penetrate the skin; Burnett and Shah require that their compositions cause the active agent to penetrate the skin. A modification of the compositions disclosed in any of Burnett or Shah, alone or in combination, would change the principle of operation of the composition disclosed therein. Therefore, the modification is impermissible under 35 U.S. C. §103(a).

Accordingly, claims 1-13 and 17 are non-obvious over the combination of Burnett and Shah.

Allowance of all claims 1-17 is earnestly solicited.

Respectfully submitted,

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